Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 9, Issue, 12, pp.63375-63379, December, 2017

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

ISSN: 0975-833X

RESEARCH ARTICLE

CORRELATION OF hsCRP TO CAROTID INTIMA MEDIA THICKNESS IN ACUTE ISCHEMIC STROKE

***Yogitha, C. and Abhinaya Varidi Reddy**

Department of Medicine, Kempegowda Institute of Medical Sciences, Bengaluru

ARTICLE INFO

Article History:
Received 28th September, 2017
Received in revised form
23rd October, 2017
Accepted 07th November, 2017
Published online 31st December, 2017

Key words:
hsCRP,
Carotid intima media thickness,
Acute ischemic stroke.

ABSTRACT

Background: Incidence and prevalence of stroke has risen exponentially worldwide in last few decades and incidence of stroke is also rising among Indians. Carotid intima media thickness (CIMT) is a non-invasive test for assessment of atherosclerosis in different arteries. There is a direct correlation with incidence of stroke. Systemic inflammation is now thought to be a part of the process for accelerated atherosclerosis. Measurements of the marker of systemic inflammation, i.e. hsCRP, may provide a good indication of the risk to develop stroke.

Objectives: To measure the hsCRP and carotid intima media thickness in patients with ischemic stroke and to establish the correlation of hsCRP to carotid intima media thickness in patients with ischemic stroke.

Methods: An observational study done at Kempegowda institute of medical sciences, Bangalore over a period of 18 months that included established cases of ischemic stroke diagnosed on the basis of clinical history, examination and neuroimaging. 60 cases of ischemic stroke aged 45 yrs or more were taken, hsCRP and Carotid intima media thickness were measured. Data were collected through a proforma specially designed for this study where patients detailed history, clinical examination and laboratory investigations were collected. Individuals with acute ischemic stroke over 45years of age, confirmed by CT scan or MRI scan were included in the study. Exclusion criteria were for the patients with hemorrhagic stroke, cerebral emboli of cardiac origin diagnosed clinically and by ECG and echo, patients on statins, patients with meningitis, brain abscess and other intracranial infections or other space occupying lesions. Patients with head injury, post operative patients suffering from rheumatoid arthritis, ankylosing spondylitis, chronic infection and inflammatory conditions.

Results: Out of 60 patients, 63.3% were hypertensive and 50% were smokers. 72% of our patients had high Carotid intima media thickness (CIMT). CIMT was significantly related to hsCRP, LDL, HDL levels and age of the patient.

Conclusion: This study has shown a significant association between CIMT and the atherogenic variables like age, hsCRP, HDL and LDL.This may indicate the need to screen patients for these risk factors. Also, in places where CIMT measurement is not available, these blood tests can be used as surrogate markers to define the patient population at risk of ischemic stroke. Conversely, in patients with ischemic stroke, these markers can be used to monitor and prevent further events by appropriate interventions.

Citation: Yogitha, C. and Abhinaya Varidi Reddy, 2017. "Correlation of hsCRP to carotid intima media thickness in acute ischemic stroke", *International Journal of Current Research*, 9, (12), 63375-63379.

INTRODUCTION

Stroke being ischemic and hemorrhagic is a common and devastating disorder. Presently, ischemic heart disease and stroke are the leading cause of mortality worldwide. More than 80% of deaths occur in the low and the middle income countries. Occurance of stroke has risen exponentially worldwide in last few decades and incidence of stroke is also rising among Indians population. Incidence of stroke increases with increasing age and with the growing elderly population, the number are likely to increase (Abhinav Goyal and Salim Yusuf, 2007; Smith *et al*., 2005). Atherosclerosis is the underlying pathophysiological cause of ischemic strokes. The risk factors may be modifiable and non-modifiable. Modifiable risk factors are mostly related to the atherosclerotic burden which includes diabetes, hypertension, smoking, and hyperlipidemia. A number of risk prediction scoring systems have been evolved to identify individuals with high risk. However, most of these scoring systems have some limitations. The carotid intima-media thickness (CIMT) has emerged as a reliable independent marker of cardiovascular events (Libby, 2005; De Silva *et al*., 2007). Carotid intima media thickness (CIMT) is used as a non-invasive test for assessment of degree of atherosclerosis in different arteries. It has been found to have direct correlation with incidence of stroke. Systemic

Corresponding author:* **Yogitha, C.
Department of Medicine, Kempegowda Institute of Medical Sciences, Bengaluru

inflammation is now thought to be part of the process for accelerated atherosclerosis. Measurements of the marker of systemic inflammation, i.e. hsCRP, may provide a good indication of risk to develop stroke. We designed a study to measure hsCRP and carotid intima media thickness in patients with ischemic stroke and also to establish the correlation of hsCRP to carotid intima media thickness in patients with ischemic stroke.

MATERIALS AND METHODS

Our objective is to measure the different blood parameters and CIMT in patients of acute ischemic stroke; and to correlate the blood parameter values with the CIMT. This cross sectional, observational study been done at Kempegowda institute of medical sciences, Bangalore. Study was conducted for a period of 18 months that included established cases of ischemic stroke diagnosed on the basis of clinical history, examination and neuroimaging. 60 cases of ischemic stroke aged 45 yrs or more were taken; hsCRP and Carotid intima media thickness were measured. Data were collected through a proforma specially designed for this study where patients detailed history, clinical examination and laboratory investigations were collected. Individuals with acute ischemic stroke over 45years of age, confirmed by CT scan or MRI scan were included in the study. Exclusion criteria were for the patients with hemorrhagic stroke, cerebral emboli of cardiac origin diagnosed clinically and by ECG and echo, patients on statins, patients with meningitis, brain abscess and other intracranial infections or other space occupying lesions .Patients with head injury, post operative patients suffering from rheumatoid arthritis, ankylosing spondylitis, chronic infection and inflammatory conditions. Sixty patients of acute ischemic stroke admitted in KIMS hospital, Bangalore were taken in this study. The study had the approval of the ethics board from the Institution. In all patients, CT-scan or MRI demonstration of cerebral infarct were required. Detailed history and clinical examination was recorded for all the patients. Laboratory investigations performed include estimation of fasting and postprandial blood sugars, lipid profile (total cholesterol, LDL, HDL, triglyceride), hsCRP levels. hsCRP was estimated using the immunoturbidimetric method. The normal value of hsCRP was taken as 1 mg/L[5]. As for CIMT, which was used as the marker for extent of atherosclerosis, doppler study of bilateral carotid arteries was performed using a high-resolution 7.5 MHz phased-array transducer.

All examinations were carried out in a dark, quiet and temperature-controlled room. With the head in a slightly bent position towards the opposite site of the one being scanned, the ultrasound transducer was placed in an angle of 90° of the vessel wall, to obtain parallel echo lines of the intima and media in both near and far walls. Imaging of both common carotid arteries (CCA) up to their bifurcation, the carotid bulb, as well as proximal 10 mm of internal carotid artery (ICA) of both sides was performed. The best images of far wall of the arteries were taken for measurement, mainly CCA. The depth of the scan was adjusted and the transmit focus zone set at the optimal level to show the best possible image of the far wall of the CCA. The ideal place of measurement of IMT was an area of at least 1 cm devoid of plaques. The presence of plaques was noted. Plaques were defined as focal widening relative to the adjacent segment, with protrusion into the lumen. Mean measured values of CIMT of three sites of a particular side were taken for calculation of CIMT of that side. IMT was finally calculated as the mean IMT of the left and right CCA. The cut off for normal CIMT was taken as 0.8 mm. In different studies, this cut-off has been found to correlate with vascular risks (Winter *et al*., 1999). This cut off is found very appropriate to predict risk also among Indians (Abdelmouttaleb *et al*., 1999). The measurements were manual and no software was used due to limited resources. All the measurements were done by a single operator, to avoid interobserver variation.

Statistical Analysis

The following methods of statistical analysis have been used in this study. The results for each parameter (numbers and percentages) for discrete data and average (mean + standard deviation) for continuous data are presented in Table and Figure.

1)Univariate analyses of the dichotomous variables encoded was performed by means of the Chi square test with Yates correction if required

Student "t' test

The student't' test was used to determine whether there was a statistical difference between groups in the parameters measured.

RESULTS

In this present study, the patient's age ranged from 45 to 80 years with ischemic stroke. Maximum number of individuals were age group of 51-70 years. The mean age was 59.82 ±8.63. 63.3% were males and 36.7% were females. Symptoms of weakness were seen in 95% of individuals. Cranial nerve involvement and speech disturbance were present in 35% and 28% respectively. Altered sensorium and seizures were present in 18% and 15% respectively. Sensory symptoms were present in 1.7% only. 63% were hypertensives, 36% were diabetics and 50% were smokers. Among 22 diabetic patients, females were 50% as similar to males. Thirty patients (50%) were smokers among which 29 were males and 1 was female. In the present study, infarct was in the MCA territory in 83.3%, ACA territory in 6.7%, PCA territory in 1.7%, MCA-PCA territory in 6.7%, MCA-ACA territory in 1.7%. In most of the subjects, MCA was involved. Among the 60 individuals, 44 (73%) had high hsCRP and 16 (26%) had normal hsCRP. 72% had high CIMT and 28% had normal CIMT. There were totally 9 patients who had plaques. All of them had high CIMT and high hsCRP. In the age group 45-50 yrs, there were 10 patients of which 5 had normal CIMT and 5 had high CIMT. In the age group 51-60 yrs, there were 23 individuals of which 11 had normal CIMT and 12 had high CIMT. In the age group 61-70 yrs, there were 23 individuals of which only 1 had normal CIMT and 22 had high CIMT. In the age group 71-80 yrs, there were 4 individuals of which none of them had normal CIMT and all 4 had high CIMT. Thus as the age is increasing, number of the individual with normal CIMT is decreasing and number of patients with high CIMT is increasing. The mean age in normal CIMT group is 53.0 and in the high CIMT group is 62.5 and it is statistically significant, p value being <0.001.Among 38 males, 13 (34%) had normal CIMT and 25 (65%) had high CIMT. Among 22 females, 4 (18%) had normal CIMT and 18 (81%) had high CIMT. Percentage of females (81%) with high CIMT was more compared to males (65%).

Distribution of Carotid intima media thickness (CIMT) and its relation with the study risk factors

Number of patients with diabetes, hypertension and smoking in high CIMT group were more compared to the normal CIMT group. But the p value was not significant being 0.649, 0.890, 0.390 for diabetes, hypertension and smoking respectively. Mean FBS in normal CIMT group was 115.12 and in high CIMT group was 122.12. Mean FBS was more in the high CIMT group compared to the low CIMT group, but there was no statistical significance p value being 0.19.

Comparison of mean PPBS values among CIMT groups

Mean PPBS in normal CIMT group was 182.47 and in high CIMT group was 186.56. The mean of PPBS was high in the high CIMT group compared to the low CIMT group but there was no statistical significance p value being 0.50.

Comparison of mean HDL values among CIMT groups

Mean value of HDL in normal group was 42.12 and in the high group it was 32.67. So the mean value of HDL was low in the high CIMT group compared to normal CIMT group. It was also statistically significant p value being less than 0.001.

Comparison of mean LDL values among CIMT groups

Mean LDL was 104.88 in normal CIMT group and in the high CIMT group, it was 129.72. Mean value of LDL was higher in the high CIMT group compared to the normal CIMT group. The p value was also significant being less than 0.001.

Comparison of mean triglyceride values among CIMT groups

Mean value of triglyceride was 146.00 in normal CIMT group and in the high CIMT group it was 152.86. Mean value of Triglyceride was higher in the high CIMT group compared to the normal CIMT group but the p value was not statistically significant being 0.197.

Comparison of mean total cholesterol values among CIMT groups

Mean value of total cholesterol was 209.47 in normal CIMT group and in the high.CIMT group it was 217.05. Mean value of Total Cholesterol was higher in the high CIMT group compared to the normal CIMT group but the p value was not statistically significant being 0.219

Comparision of hsCRP and CIMT

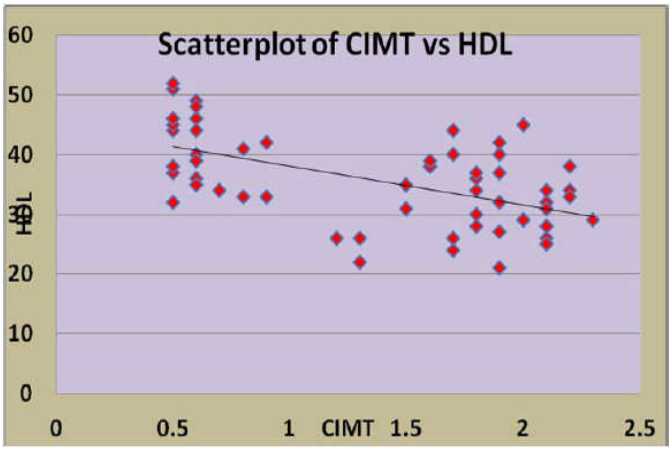
CIMT was normal in 17 patients. Among them, 94.1% had normal hsCRP and only 5.9% had high hsCRP. CIMT was high in 43 patients and all of them had high hsCRP.

Comparision of mean hsCRP values among CIMT groups

The mean value of hsCRP in normal CIMT group is 0.659 and in the high CIMT group is 3.656. The difference was statistically significant between the CIMT groups p value being less than 0.001. The mean values of FBS, PPBS, LDL, Triglyceride, Total Cholesterol, hsCRP in high CIMT group are more compared to normal CIMT group. The mean value of HDL was less in high CIMT group compared to normal CIMT group. p value is significant for HDL, LDL, hsCRP being <0.001 for all the three variables. The correlation coefficient is highest for hsCRP being 0.909, being almost equal to 1. (Table 1)

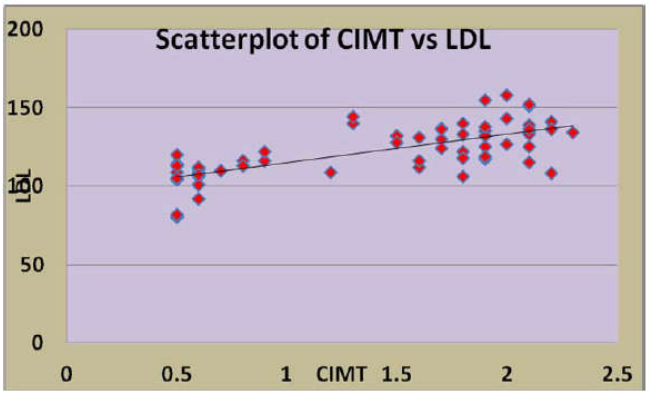
Table 1. Comparison of the investigatory findings of ischemic stroke patients with high Carotid Intima Media Thickness (CIMT) with normal CIMT

Parameter	CIMT groups	N	Mean	SD	P value (t test)	Correlation coefficient with high CIMT
FBS(mg/dl)	<0.8	17	115.12	18.560	0.190	r=0.272;p=0.035
	>=0.8	43	122.12	18.359		
PPBS(mg/dl)	<0.8	17	182.47	15.553	0.509	NS
	>=0.8	43	186.56	23.355		
HDL(mg/dl)	<0.8	17	42.12	6.214	***<0.001***	NS
	>=0.8	43	32.67	6.186		
LDL(mg/dl)	<0.8	17	104.88	10.799	***<0.001***	r=0.708;p***<0.001***
	>=0.8	43	129.72	12.901		
Triglyceride(mg/dl)	<0.8	17	146.00	11.424	0.197	r=0.156;p=0.234
	>=0.8	43	152.86	20.359		
Total Cholestrol(mg/dl)	<0.8	17	209.47	12.140	0.219	***r=0.198;p=0.129***
	>=0.8	43	217.05	23.887		
hs CRP(mg/l)	<0.8	17	0.659	0.166	***<0.001***	r=0.909;p***<0.001***
	>=0.8	43	3.656	1.323		



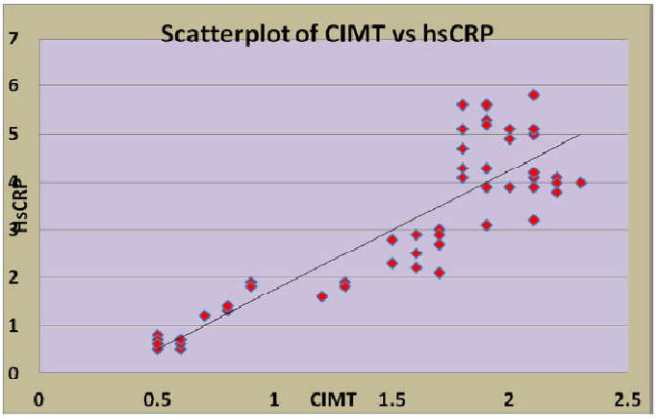
Graph 1. Correlation of CIMT to HDL

Correlation of CIMT to HDL is negative that is, as the CIMT increases HDL decreases.



Graph 2. Correlation of CIMT to LDL

Correlation of CIMT to LDL is positive that is, as CIMT increases LDL also increases with the correlation coefficient being r=0.708.



Graph 3. Correlation of CIMT to hsCRP

Correlation of CIMT to hsCRP is positive that is, as CIMT increases hsCRP also increases with the correlation coefficient being (r=0.909) very strong almost nearings 1.

DISCUSSION

A total of 60 patients with acute ischemic stroke were studied. Maximum number of patients (n=23) 38.3% were in the age group of 51-60 years and 61-70 years respectively in each group. The mean age was 59.82 ±8.63. This is comparable to the Bangalore study where in the mean age was 54.5 years (Nagaraja *et al*., 2009). In contrast, in a population based study by Dalal *et al*. (Population-Based Stroke Survey in Mumbai, India, 2008) in Mumbai the mean age for stroke was 66 years, and in Trivandrum by Sridharan *et al*. (2009) the median age was 67 years. About two thirds of the patients were males (n=38, 63.3%). The Bangalore study also showed a greater preponderance among men (67%) with a male to female ratio of 2:1 (Abdelmouttaleb *et al*., 1999). The major presenting symptom was weakness in 57(95%) followed by cranial nerve involvement and speech disturbance which were present in 35% and 28% respectively. Sensory symptoms were present in very few number of patients i.e, (n=4) 6.6% only. This is comparable with Bangalore study where in Weakness or paresis (92%) was the commonest presentation (Abdelmouttaleb *et al*., 1999). Most of the patients had infarct in the MCA territory (n=50) 83.3% and the least involved were PCA and MCA-ACA territories with 1 patient in each 1.7%. In this study, we found 72% prevalence of high CIMT in patients with acute ischemic stroke. This is comparable to the study by Avishek saha *et al* in which the prevalence for high CIMT in ischemic stroke patients was 72% (Pradip *et al*., 2011). The patients were divided into two groups: - those with high CIMT (n=43) and those with normal CIMT (n=17). In the age groups 45-60 yrs there were almost equal number of patients in both the groups but in the age groups 61-80 yrs number of patients in high CIMT group (n=26) 96% outnumbered those in normal CIMT group (n=1) 3.7%. Thus as the age is increasing number of the subjects with normal CIMT is decreasing and number of subjects with high CIMT is increasing. It is statistically significant with a p value of *<0.001*. CIMT is age dependent and increases at a rate of 0.005-0.010 mm/year (O'Leary and Bots, 2010). Table compares the laboratory values of the groups with high and normal CIMT. As shown, of the ischemic stroke patients studied, hsCRP and LDL levels were significantly higher while HDL-C values were significantly lower in patients with high CIMT. The mean age of patients with high CIMT was significantly older than those with normal CIMT. Fasting blood sugar levels were also higher in patients with high CIMT as compared to patients with normal CIMT. The difference was not significance (p=0.190) by chi square test but the correlation coefficient was positive being r=0.272. High CIMT was significantly related to vascular risk factors such as age, HDL, LDL, serum hsCRP. Of all the parameters, there was positive correlation between serum hsCRP r=0.909, LDL r= 0.708, FBS r=0.272, triglyceride r=0.156, total cholesterol r=0.198 and CIMT. There was also association of hypertension, smoking and diabetes with high CIMT, but these were not statistically significant. There were not many studies of risk factors for stroke from India. The study by Gupta *et al*. (2008) found tobacco use, obesity with high waist: hip ratio, high blood pressure, high LDL cholesterol, low HDL cholesterol, abnormal apolipoprotein A-1:B ratio, diabetes, low consumption of fruits and vegetables, sedentary lifestyles and psychosocial stress to correlate with vascular events. In a study by Avishek Saha *et al*. (Pradip K Sinha *et al*., 2011), the patients of ischemic stroke had high levels of fibrinogen, hsCRP, homocysteine and LDL. In our study, we found that our patients of ischemic stroke had high levels of hsCRP and LDL. The Rotterdam study showed that increasing CIMT is a risk factor for stroke; analogous to coronary plaques in acute myocardial infarction (Bots *et al*., 1997). These associations were independent of age, sex, and history of myocardial infarction or stroke. The noninvasive assessment of common carotid intima-media thickness may thus be a promising method to assess the degree of atherosclerosis, in populations at large.

A study by Cao *et al* showed that C-reactive protein level is an independent risk factor for ischemic stroke, and it has even higher risk in the presence of high CIMT (Cao *et al*., 2003). In the study by Avishek Saha *et al*, they found that in the group with high CIMT, the hsCRP level was significantly higher as compared to the group with normal CIMT (2.27 ± 1.77 g/L vs. 0.795± 0.34; p=0.0012) (Pradip K Sinha *et al*., 2011). In our study we found that in the group with high CIMT, the hsCRP level was significantly higher as compared to the group with normal CIMT (3.656 ± 1.32 vs. 0.659 ± 0.16; p*<0.001*). C-reactive protein is not just a risk marker. It has been shown to play an active role in atherogenesis (Torzewski *et al*., 2000). C-reactive protein is chemotactic for freshly isolated human blood monocytes. A specific C-reactive protein receptor is demonstrated on monocytes in vitro as well as in vivo, and blockage by use of a monoclonal antireceptor antibody completely abolishes CRP-induced chemotaxis. CRP may thus play a major role in the recruitment of monocytes during atherogenesis (Torzewski *et al*., 2000). We also found significant association between serum HDL, LDL levels and CIMT. These risk factors of atherosclerosis are well established. A Finnish study has shown association between LDL and CIMT. In the Muscatine study, a risk factor load model showed relation between HDL and CIMT (Davis *et al*., 2001). However, although the new risk factors have significant associations with atherosclerosis and hence the risk of developing ischemic stroke, it may not mean that these should be screened in all in the general populations. Some working groups have proposed that only patients classified as 'high' or at least 'intermediate' risk be screened with these markers to find the additional risk burden (Ridker, 1999).

Limitation

This is a crosssectional study having limitation of low number of patients. For better determining the association between

these variables, we need a prospective study with serial follow ups. The studies such as by Cao *et al* give better idea of the true risk. Also, the manual measurement technique used in this study was inferior to the automated software based methods of IMT measurement, which can simultaneously take multiple measurements.

Conclusion

Study has shown a significant association between CIMT and the atherogenic variables like age, hsCRP, HDL and LDL. This may indicate the need to screen patients for these risk factors. Also, in places where CIMT measurement is not available, these blood tests can be used as surrogate markers to define the patient population at risk of ischemic stroke. Conversely, in patients with ischemic stroke, these markers can be used to monitor and prevent further events by appropriate interventions.

Summary

This study is an observational descriptive study carried out to emphasise the importance of novel risk factor like hsCRP and its correlation with CIMT in the setting of an acute ischemic stroke. Study was carried out in the premises of kempegowda institute of medical sciences hospital during an 18 months period. 60 cases of acute ischemic stroke were selected in random basis, CIMT, serum hsCRP and other blood investigations like FBS , PPBS , lipid profile were done . The prevalence of high CIMT was found to be 72% and that of hsCRP was 73%. The association between CIMT and various risk factors were studied. There was association of hypertension, smoking and diabetes with high CIMT, but these were not statistically significant. Fasting blood sugar levels were also higher in patients with high CIMT as compared to patients with normal CIMT. But the difference was not statistically significant. There was a positive correlation between CIMT and FBS, LDL, Triglyceride, Total Cholestrol, hsCRP.A significant association between CIMT and the atherogenic variables likeage, hsCRP, HDL and LDL was found. This may indicate the need to screen patients for these risk factors.

Acknowledgement

We sincerely thank all the individuals who have supported us for the study. We thank Mr Pradeep B K (Biocon) for scientific assistance.

REFERENCES

Abdelmouttaleb I, Danchin N, Ilardo C, Aimone-Gastin I, Angioï M, Lozniewski A. *et al*. 1999. C-Reactive protein and coronary artery disease: Additional evidence of the implication of an inflammatory process in acute coronary syndromes. *Am Heart J*., 137(2):346–51

Abhinav Goyal and Salim Yusuf. 2007. The burden of cardiovascular disease in the Indian subcontinent. *Indian J Med Res*., 124:235-44.

Biasucci LM, Liuzzo G, Grillo RL, Caligiuri G, Rebuzzi AG, Buffon A. *et al*. 1999. Elevated levels of C-reactive protein at discharge in patients with unstable angina predict recurrent instability. Circulation, 23;99(7):855–60.

Bots ML, Hoes AW, Koudstaal PJ, Hofman A. and Grobbee DE. 1997. Common Carotid Intima-Media Thickness and Risk of Stroke and Myocardial Infarction. Circulation. 96(5):1432–7.

Cao JJ, Thach C, Manolio TA, Psaty BM, Kuller LH, Chaves PHM. *et al*. 2003. Creactive Protein, Carotid Intima-Media Thickness, and Incidence of Ischemic Stroke in the Elderly. Circulation, 108(2):166–70.

Davis PH, Dawson JD, Riley WA. and Lauer RM. 2001. Carotid intimal-medial thickness is related to cardiovascular risk factors measured from childhood through middle age: The Muscatine Study. Circulation, 104(23):2815–9.

De Silva DA, Woon FP, Lee MP, Chen CP, Chang HM. and Wong MC. 2007. South Asian patients with ischemic stroke intracranial large arteries are the predominant site of disease. Stroke, 38:2592-4.

Gupta R, Joshi P, Mohan V, Reddy KS. and Yusuf S. 2008. Epidemiology and causation of coronary heart disease and stroke in India. Heart, 94(1):16–26.

Libby P. 2005. Prevention and treatment of atherosclerosis. In: Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson JL, editors. Harrison's principles of Internal Medicine. 16th ed. McGraw-Hill Companies, p. 1430-3.

Nagaraja D, Gururaj G, Girish N, Panda S, Roy AK, Sarma GRK, *et al*. 2009. Feasibility study of stroke surveillance: Data from Bangalore, India. http://icmr.nic.in/ijmr/2009/October/1007.pdf [Internet]. Available from: http://imsear.hellis.org/handle/123456789/135910

O'Leary DH. and Bots ML. 2010. Imaging of atherosclerosis: carotid intima-media thickness. *Eur Heart J*., (14):1682–9.

Population-Based Stroke Survey in Mumbai, India: Incidence and 28-Day Case Fatality - Abstract - Neuroepidemiology 2008, Vol. 31, No. 4 – Karger Publishers [Internet]. Available from: http://www.karger.com/Article/Abstract/165364

Pradip K Sinha MD DM, Rudrajit Paul, Ramtanu Bandyopadhyay MD, Koushik Biswas and Amit K Banerjee, 2011. Study of carotid intima media thickness and its correlation with novel risk factors in ischemic stroke [Internet]. *Neurology Asia*, 16(1): 25 – 31.

Ridker PM. 1999. Evaluating novel cardiovascular risk factors: can we better predict heart attacks? *Ann Intern Med*., 130(11):933–7.

Smith WS, Johnston SC. and Easton DJ. 2005. Cerebrovascular diseases. In: Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson LJ, editors. Harrison's principles of Internal Medicine. 16th ed. McGraw-Hill Companies, p. 2372-93.

Sridharan SE, Unnikrishnan JP, Sukumaran S, Sylaja PN, Nayak SD, Sarma PS. *et al*. 2009. Incidence, Types, Risk Factors, and Outcome of Stroke in a Developing Country. Stroke, 40(4):1212–8.

Torzewski M, Rist C, Mortensen RF, Zwaka TP, Bienek M, Waltenberger J. *et al*. 2000. C-Reactive Protein in the Arterial Intima. *Arterioscler Thromb Vasc Biol*., 20(9): 2094–9.

Winter RJ, Bholasingh R, Lijmer JG, Koster RW, Gorgels JP, Schouten Y. *et al*. 1999. Independent prognostic value of C-reactive protein and troponin I in patients with unstable angina or non-Q-wave myocardial infarction. *Cardiovasc Res*., 42(1):240–5.

****